ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Yescarta 0.4 – 2 x 10^8 cells dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Yescarta (axicabtagene ciloleucel) is a CD19-directed genetically modified autologous T cell immunotherapy. To prepare Yescarta, patient's own T cells are harvested and genetically modified *ex vivo* by retroviral transduction to express a chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment linked to CD28 co-stimulatory domain and CD3-zeta signalling domain. The anti-CD19 CAR-positive viable T cells are expanded and infused back into the patient, where they can recognise and eliminate CD19-expressing target cells.

2.2 Qualitative and quantitative composition

Each patient specific single infusion bag of Yescarta contains a dispersion of anti-CD19 CAR T cells in approximately 68 mL for a target dose of 2 x 10^6 anti-CD19 CAR-positive viable T cells/kg body weight (range: 1 x 10^6 – 2 x 10^6 cells/kg), with a maximum of 2 x 10^8 anti-CD19 CAR T cells.

Excipients with known effect

Each bag of Yescarta contains 300 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for infusion.

A clear to opaque, white to red dispersion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Yescarta is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

Yescarta is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy.

4.2 Posology and method of administration

Yescarta must be administered in a qualified treatment centre by a physician with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with Yescarta. At least 1 dose of tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available prior to infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion.

Posology

Yescarta is intended for autologous use only (see section 4.4).

A single dose of Yescarta contains 2 x 10^6 CAR-positive viable T cells per kg of body weight (or maximum of 2 x 10^8 CAR-positive viable T cells for patients 100 kg and above) in approximately 68 mL dispersion in an infusion bag.

The availability of Yescarta must be confirmed prior to starting the lymphodepleting regimen.

Pre-treatment (lymphodepleting chemotherapy)

- A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m^2 intravenous and fludarabine 30 mg/m^2 intravenous must be administered prior to infusing Yescarta. The recommended days are on the 5^{th}, 4^{th}, and 3^{rd} day before infusion of Yescarta.

Pre-medication

- Paracetamol 500-1 000 mg given orally and diphenhydramine 12.5 to 25 mg intravenous or oral (or equivalent) approximately 1 hour before Yescarta infusion is recommended.
- Prophylactic use of systemic corticosteroids is not recommended as it may interfere with the activity of Yescarta.

Monitoring

- Patients must be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs or symptoms of CRS and/or neurologic events.
- After the first 10 days following the infusion, the patient is to be monitored at the physician's discretion.
- Patients must be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion.

Special populations

Patients with human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) infection

There is no clinical experience in patients with active HIV, HBV or HCV infection.

Paediatric population

The safety and efficacy of Yescarta in children and adolescents below 18 years of age have not yet been established. No data are available.

Elderly

No dose adjustment is required in patients ≥ 65 years of age. Efficacy was consistent with the overall treated patient population.

Method of administration

Yescarta is to be administered via intravenous infusion.

Yescarta must not be irradiated. Do NOT use a leukodepleting filter.

Precautions to be taken before handling or administering the medicinal product
This medicinal product contains genetically modified human blood cells. Healthcare professionals handling Yescarta must take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases.

Preparation for infusion
- Verify that the patient's identity (ID) matches the patient identifiers on the Yescarta cassette.
- The Yescarta bag must not be removed from the metal cassette if the information on the patient-specific label does not match the intended patient.
- Once the patient ID is confirmed, remove the Yescarta bag from the metal cassette.
- Check that the patient information on the metal cassette label matches that on the bag label.
- Inspect the product bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines for the handling of waste of human-derived material (or immediately contact Kite).
- Place the infusion bag inside a second bag.
- Thaw Yescarta at approximately 37 °C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Yescarta must not be washed, spun down, and/or re-suspended in new medium prior to infusion. Thawing takes approximately 3 to 5 minutes.
- Once thawed, Yescarta is stable at room temperature (20 °C-25 °C) for up to 3 hours. However, Yescarta infusion must begin within 30 minutes of thaw completion.

Administration
- For autologous use only.
- Tocilizumab and emergency equipment must be available prior to infusion and during the monitoring period. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, suitable alternative measures to treat CRS instead of tocilizumab must be available prior to infusion.
- A leukodepleting filter must not be used.
- Central venous access is recommended for the administration of Yescarta.
- Verify the patient ID again to match the patient identifiers on the Yescarta bag.
- Prime the tubing with 0.9% sodium chloride solution (0.154 mmol sodium per mL) prior to infusion.
- Infuse the entire content of the Yescarta bag within 30 minutes by either gravity or a peristaltic pump.
- Gently agitate the bag during Yescarta infusion to prevent cell clumping.
- After the entire content of the bag is infused, rinse the tubing at the same infusion rate with 0.9% sodium chloride solution (0.154 mmol sodium per mL) to ensure all Yescarta is delivered.

For instructions on the handling, accidental exposure to and disposal of the medicinal product, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Contraindications of the lymphodepleting chemotherapy must be considered.

4.4 Special warnings and precautions for use

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient must be kept for a period of 30 years after expiry date of the product.

General

Yescarta is intended solely for autologous use and must not be administered to other patients. Before infusion, the patient's identity must match the patient identifiers on the Yescarta infusion bag and cassette. Do not infuse Yescarta if the information on the patient-specific label does not match the intended patient.

Patients must be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurologic events. After the first 10 days following infusion, the patient is to be monitored at the physician's discretion.

Counsel patients to remain within the proximity of a qualified treatment centre for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of CRS or neurological adverse reactions occur. Monitoring of vital signs and organ function must be considered depending on the severity of the reaction.

Reasons to delay treatment

Due to the risks associated with Yescarta treatment, infusion must be delayed if a patient has any of the following conditions:

- Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions, or hypotension) including from preceding chemotherapies.
- Active uncontrolled infection.
- Active graft-versus-host disease (GVHD).

Serological testing

Screening for HBV, HCV, and HIV must be performed before collection of cells for manufacturing of Yescarta (see section 4.2).

Blood, organ, tissue and cell donation

Patients treated with Yescarta must not donate blood, organs, tissues, or cells for transplantation.

Concomitant disease

Patients with active CNS disorder or inadequate renal, hepatic, pulmonary, or cardiac function are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention.

Primary central nervous system (CNS) lymphoma

There is no experience of use of Yescarta in patients with primary CNS lymphoma. Therefore, the risk/benefit of Yescarta has not been established in this population.

Cytokine release syndrome

Nearly all patients experienced some degree of CRS. Severe CRS, including life-threatening and fatal reactions, was very commonly observed with Yescarta with a time to onset of 1 to 12 days in ZUMA-1 and 1 to 11 days in ZUMA-5 (see section 4.8). CRS should be managed at the physician's discretion, based on the patient's clinical presentation and according to the CRS management algorithm provided in Table 1. Interleukin-6 (IL-6) receptor inhibitor based therapy such as tocilizumab has been administered for moderate or severe CRS associated with Yescarta.

At least 1 dose of tocilizumab per patient must be on site and available for administration prior to Yescarta infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicine Agency shortage catalogue, the treatment centre must have access to suitable alternative measures instead of tocilizumab to treat CRS.

Monitor patients daily for signs and symptoms of CRS for at least 10 days following infusion at the qualified clinical facility. After the first 10 days following infusion, the patient is to be monitored at the physician's discretion.

Counsel patients to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of CRS occur. Treatment algorithms have been developed to ameliorate some of the CRS symptoms experienced by patients on Yescarta. These include the use of tocilizumab or tocilizumab and corticosteroids for moderate, severe, or life-threatening CRS as summarised in Table 1. Patients who experience Grade 2 or higher CRS (e.g. hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) must be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening- CRS, consider intensive-care supportive therapy.

Yescarta must not be administered to patients with active infections or inflammatory disease until these conditions have resolved.

CRS has been known to be associated with end organ dysfunction (e.g., hepatic, renal, cardiac, and pulmonary). In addition worsening of underlying organ pathologies can occur in the setting of CRS. Patients with medically significant cardiac dysfunction must be managed by standards of critical care and measures such as echocardiography are to be considered.

Diagnosis of CRS requires excluding alternate causes of systemic inflammatory response, including infection. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

Evaluation for haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) is to be considered in patients with severe or unresponsive CRS.

Yescarta continues to expand and persist following administration of tocilizumab and corticosteroids. Tumour necrosis factor (TNF) antagonists are not recommended for management of Yescarta-associated CRS.

Table 1: CRS grading and management guidance

CRS Grade[a]	Tocilizumab	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	If not improving after 24 hours, manage as Grade 2.	N/A
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO_2 or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity[b].	Administer tocilizumab[c] 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24 hour period; maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS, or if no response to second or subsequent doses of tocilizumab, consider alternate measures for treatment of CRS.	Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO_2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours). Continue corticosteroids use until the event is Grade 1 or less, then taper. If not improving, manage as Grade 4 (below).
Grade 4 Life-threatening symptoms. Requirements for ventilator support or continuous veno-venous haemodialysis or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	Administer methylprednisolone 1 000 mg intravenously per day for 3 days; if improves, then manage as above. Consider alternate immunosuppressants if no improvement or if condition worsens.

N/A = not available/not applicable

a. Lee et al 2014.

b. Refer to Table 2 for management of neurologic adverse reactions.

c. Refer to tocilizumab summary of product characteristics for details.

Neurologic adverse reactions

Severe neurologic adverse reactions, also known as immune effector cell-associated neurotoxicity syndrome (ICANS) have been very commonly observed in patients treated with Yescarta, which could be life-threatening or fatal (see section 4.8). Patients with a history of CNS disorders such as seizures or cerebrovascular ischaemia may be at increased risk. Fatal and serious cases of cerebral oedema have been reported in patients treated with Yescarta. Patients must be monitored for signs and symptoms of neurologic adverse reactions (Table 2). Patients must be monitored at least daily for 10 days at the qualified healthcare facility following infusion for signs and symptoms of neurologic toxicity/ICANS. After the first 10 days following the infusion, the patient is to be monitored at the physician's discretion. Counsel patients to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of

neurologic toxicity/ICANS occur. Monitoring of vital signs and organ functions must be considered depending on the severity of the reaction.

Patients who experience Grade 2 or higher neurologic toxicities /ICANS must be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive-care supportive therapy for severe or life-threatening neurologic toxicities. Non-sedating, anti-seizure medicines are to be considered for seizure prophylaxis as clinically indicated for Grade 2 or higher adverse reactions. Treatment algorithms have been developed to ameliorate the neurologic adverse reactions experienced by patients on Yescarta. These include the use of tocilizumab (if concurrent CRS) and/or corticosteroids for moderate, severe, or life-threatening neurologic adverse reactions as summarised in Table 2.

Table 2: Neurologic adverse reaction/ICANS grading and management guidance

Grading assessment	**Concurrent CRS**	**No concurrent CRS**
Grade 2	Administer tocilizumab per Table 1 for management of Grade 2 CRS. If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 3	Administer tocilizumab per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4	Administer tocilizumab per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1 000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1 000 mg intravenously per day for 2 more days; if improves, then manage as above. If not improving, consider 1 000 mg of methylprednisolone intravenously 3 times a day or alternate therapy[a]	Administer methylprednisolone 1 000 mg intravenously per day for 3 days; if improves, then manage as above. If not improving, consider 1 000 mg of methylprednisolone intravenously 3 times a day or alternate therapy.[a]
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

a. Alternate therapy includes (but is not limited to): anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG and ATG.

Infections and febrile neutropenia

Serious infections have been very commonly observed with Yescarta (see section 4.8). Patients must be monitored for signs and symptoms of infection before, during, and after Yescarta infusion and treated appropriately. Prophylactic anti-microbials should be administered according to standard institutional guidelines.

Febrile neutropenia has been observed in patients after Yescarta infusion (see section 4.8) and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

HBV reactivation

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs directed against B-cells. Screening for HBV, HCV, and HIV must be performed before collection of cells for manufacturing of Yescarta.

Prolonged cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Yescarta infusion. Grade 3 or higher prolonged cytopenias following Yescarta infusion occurred very commonly and included thrombocytopenia, neutropenia, and anaemia. Monitor blood counts after Yescarta infusion.

Hypogammaglobulinaemia

B-cell aplasia leading to hypogammaglobulinaemia can occur in patients receiving treatment with Yescarta. Hypogammaglobulinaemia has been very commonly observed in patients treated with Yescarta. Immunoglobulin levels should be monitored after treatment with Yescarta and managed using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement.

Hypersensitivity reactions

Allergic reactions may occur with the infusion of Yescarta. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in Yescarta.

Secondary malignancies

Patients treated with Yescarta may develop secondary malignancies. Monitor patients life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact the company to obtain instructions on patient samples to collect for testing.

Tumour lysis syndrome (TLS)

TLS, which may be severe, has occasionally been observed. To minimise risk of TLS, patients with elevated uric acid or high tumour burden should receive allopurinol, or an alternative prophylaxis, prior to Yescarta infusion. Signs and symptoms of TLS must be monitored and events managed according to standard guidelines.

Prior treatment with anti-CD19 therapy

There is limited experience with Yescarta in patients exposed to prior CD19-directed therapy. Yescarta is not recommended if the patient has relapsed with CD19-negative disease after prior anti-CD19 therapy.

Excipients

This medicinal product contains 300 mg sodium per infusion bag, equivalent to 15% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Patients are expected to enrol in a registry and will be followed in the registry in order to better understand the long-term safety and efficacy of Yescarta.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with Yescarta.

Live vaccines

The safety of immunisation with live viral vaccines during or following Yescarta treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Yescarta treatment, and until immune recovery following treatment with Yescarta.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

The pregnancy status of women of child bearing potential must be verified before starting Yescarta treatment.

See the prescribing information for lymphodepleting chemotherapy for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with Yescarta.

Pregnancy

There are no available data with Yescarta use in pregnant women. No reproductive and developmental toxicity animal studies have been conducted with Yescarta to assess whether it can cause foetal harm when administered to a pregnant woman (see section 5.3).

It is not known if Yescarta has the potential to be transferred to the foetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause foetal toxicity, including B-cell lymphocytopenia. Therefore, Yescarta is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women must be advised on the potential risks to the foetus. Pregnancy after Yescarta therapy must be discussed with the treating physician.

Assessment of immunoglobulin levels and B-cells in newborns of mothers treated with Yescarta must be considered.

Breast-feeding

It is unknown whether Yescarta is excreted in human milk or transferred to the breast-feeding child. Breast-feeding women must be advised of the potential risk to the breast-fed child.

Fertility

No clinical data on the effect of Yescarta on fertility are available. Effects on male and female fertility have not been evaluated in animal studies.

4.7 Effects on ability to drive and use machines

Yescarta has major influence on the ability to drive and use machines. Due to the potential for neurologic events, including altered mental status or seizures, patients must refrain from driving or operating heavy or potentially dangerous machines until at least 8 weeks after infusion or until resolution of neurologic adverse reactions.

4.8 Undesirable effects

Summary of the safety profile

The safety data described in this section are from a total of 227 adult patients treated with Yescarta in two multi-centre pivotal clinical studies (ZUMA-1 and ZUMA-5, which treated 108 patients with DLBCL or PMBCL and 119 patients with FL).

Diffuse Large B-cell Lymphoma and Primary Mediastinal Large B-cell Lymphoma
The safety data described in this section reflect exposure to Yescarta in ZUMA-1, a Phase 1/2 study in which 108 patients with relapsed/refractory B-cell non-Hodgkin lymphoma (NHL) received CAR-positive T cells based on a recommended dose which was weight-based. The data described are from the 54-month follow-up analysis where median actual duration of follow-up was 23.5 months (range: 0.3 to 67.8 months).

The most significant and frequently occurring adverse reactions were CRS (93%), encephalopathy (60%), and infections (40%).

Serious adverse reactions occurred in 51% of patients. The most common serious adverse reactions included encephalopathy (22%), unspecified pathogen infections (15%), bacterial infections (6%), viral infections (6%), febrile neutropenia (5%) and fever (5%).

The most common (≥5%) Grade 3 or higher non-haematological adverse reactions included encephalopathy (31%), unspecified pathogen infections (19%), CRS (11%), bacterial infection (9%), viral infection (6%), delirium (6%), hypotension (6%), transaminases increased (6%) and hypertension (6%).

Follicular Lymphoma
The safety data described in this section reflect exposure to Yescarta in ZUMA-5, a Phase 2 study in which 119 patients with relapsed/refractory FL, received CAR-positive T cells based on a recommended dose which was weight-based. The data described are from the 24-month follow-up analysis where median actual duration of follow-up was 25.9 months (range: 0.3 to 44.3 months).

The most significant and frequently occurring adverse reactions were CRS (77%), infections (59%) and encephalopathy (47%).

Serious adverse reactions occurred in 45% of patients. The most common serious adverse reactions included encephalopathy (16%), unspecified pathogen infections (12%), CRS (12%), bacterial infections (5%), fever (4%), viral infection (4%) and thrombosis (3%).

The most common (≥5%) Grade 3 or higher non-haematological adverse reactions included encephalopathy (14%), unspecified pathogen infections (11%) and CRS (6%).

Tabulated list of adverse reactions

Adverse reactions described in this section were identified in patients exposed to Yescarta in ZUMA-1 (n=108) and ZUMA-5 (n=119) and from post-marketing reports. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse drug reactions identified with Yescarta

System Organ Class (SOC)	Frequency	Adverse reactions
Infections and infestations		
	Very common	Unspecified pathogen infections Viral infections Bacterial infections
	Common	Fungal infections
Blood and lymphatic system disorders		
	Very common	Febrile neutropenia[#] Neutropenia[#] Lymphopenia[#] Leukopenia[#] Anaemia[#] Thrombocytopenia[#]
	Common	Coagulopathy[a]
Immune system disorders		
	Very common	Cytokine Release Syndrome Hypogammaglobulinaemia[n]
	Common	Hypersensitivity
	Uncommon	Haemophagocytic Lymphohistiocytosis
Metabolism and nutrition disorders		
	Very common	Hyponatraemia[#] Hypophosphatemia[#] Hyperuricemia[#] Decreased appetite[o] Weight decrease
	Common	Hypokalemia[#] Hypocalcaemia[#] Hypoalbuminaemia[#] Dehydration[p]
Psychiatric disorders		
	Very common	Delirium[y] Insomnia
	Common	Affective disorder[z]
Nervous system disorders		
	Very common	Encephalopathy[s] Tremor[u] Headache[t] Dizziness[v]
	Common	Seizures, including status epilepticus Hemiparesis Ataxia[x] Neuropathy peripheral[w]
	Uncommon	Quadriplegia Spinal cord oedema Myelitis Dyscalculia Myoclonus
Cardiac disorders		
	Very common	Tachycardia[b] Arrhythmia[c]
	Common	Cardiac arrest Cardiac failure[d]
Vascular disorders		
	Very common	Hypotension[hh] Hypertension
	Common	Thrombosis[ii]

System Organ Class (SOC)	Frequency	Adverse reactions
Respiratory, thoracic and mediastinal disorders		
	Very common	Dyspnoea[cc] Cough[bb]
	Common	Hypoxia[dd] Pleural effusion Nasal inflammation[ee]
	Uncommon	Respiratory failure[ff]
Gastrointestinal disorders		
	Very common	Vomiting Diarrhoea[f] Constipation Abdominal pain[g] Nausea
	Common	Dysphagia* Dry mouth[h]
Skin and subcutaneous tissue disorders		
	Very common	Rash[gg]
Musculoskeletal and connective tissue disorders		
	Very common	Motor dysfunction[r] Musculoskeletal pain[q]
	Uncommon	Rhabdomyolysis
Renal and urinary disorders		
	Common	Renal impairment[aa]
General disorders and administration site conditions		
	Very common	Fever[j] Oedema[k] Fatigue[i] Chills
	Common	Pain
	Uncommon	Multiple organ dysfunction syndrome
Eye Disorders		
	Common	Visual impairment[e]
Investigations		
	Very common	Transaminases increased[#l]
	Common	Hyperbilirubinemia[#m]

* Dysphagia has been reported in the setting of neurologic toxicity and encephalopathy.

[#] Frequency based on Grade 3 or higher laboratory parameter.

a. Coagulopathy includes Coagulopathy, Blood fibrinogen decreased, Disseminated intravascular coagulation, International normalised ratio increased, Prothrombin time prolonged

b. Tachycardia includes Tachycardia, Sinus tachycardia

c. Arrhythmia includes Arrhythmia, Atrial fibrillation, Atrial flutter, Atrioventricular block, Atrioventricular block first degree, Bradycardia, Bundle branch block right, Electrocardiogram QT prolonged, Electrocardiogram T wave inversion, Extrasystoles, Heart rate irregular, Sinus bradycardia, Supraventricular extrasystoles, Supraventricular tachycardia, Ventricular arrhythmia, Ventricular extrasystoles, Ventricular tachycardia

d. Cardiac failure includes Cardiac failure, Acute left ventricular failure, Ejection fraction decreased, Stress cardiomyopathy

e. Visual impairment includes Vision blurred, Visual acuity reduced

f. Diarrhoea includes Diarrhoea, Colitis, Enteritis

g. Abdominal pain includes Abdominal pain, Abdominal discomfort, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Dyspepsia, Epigastric discomfort

h. Dry mouth includes Dry mouth, Lip dry

i. Fatigue includes Fatigue, Asthenia, Decreased activity, Malaise

j. Fever includes Hyperthermia, Pyrexia

k. Edema includes Oedema, Conjunctival oedema, Face oedema, Generalized oedema, Localized oedema, Oedema genital, Oedema peripheral, Periorbital oedema, Peripheral swelling, Scrotal oedema, Swelling, Swelling face

l. Transaminases increased includes Transaminases increased, Hepatic enzyme increased, Alanine aminotransferase increased, Aspartate aminotransferase increased

m. Hyperbilirubinemia increased includes Hyperbilirubinemia, Blood bilirubin increased

n. Immunoglobulins decreased includes Hypogammaglobulinemia, Blood immunoglobulin G decreased

o. Decreased appetite includes Decreased appetite, Hypophagia

p. Dehydration includes Dehydration, Hypovolaemia

q. Musculoskeletal pain includes Arthralgia, Back pain, Bone pain, Flank pain, Groin pain, Musculoskeletal chest pain, Myalgia, Neck pain, Osteoarthritis, Pain in extremity

r. Motor dysfunction includes Motor dysfunction, Muscle rigidity, Muscle spasms, Muscle spasticity, Muscle strain, Muscular weakness
s. Encephalopathy includes Encephalopathy, Agraphia, Amnesia, Aphasia, Aphonia, Apraxia, Cognitive disorder, Confusional state, Depressed level of consciousness, Disturbance in attention, Dysarthria, Dysgraphia, Dyskinesia, Hypersomnia, Immune effector cell-associated neurotoxicity syndrome, Lethargy, Leukoencephalopathy, Loss of consciousness, Memory impairment, Mental status changes, Neurotoxicity, Somnolence, Speech disorder, Stupor
t. Headache includes Headache, Head discomfort
u. Tremor includes Tremor, Head titubation
v. Dizziness includes Dizziness, Presyncope, Syncope, Vertigo
w. Neuropathy peripheral includes, Neuropathy peripheral, Allodynia, Cervical radiculopathy, Hyperaesthesia, Hypoaesthesia, Paraesthesia, Parosmia, Peripheral motor neuropathy, Peripheral sensory neuropathy
x. Ataxia includes Ataxia, Balance disorder, Gait disturbance, Vestibular disorder
y. Delirium includes Delirium, Agitation, Delusion, Disorientation, Hallucination, Restlessness
z. Affective disorder includes Impulsive behavior, Mania, Mood altered, Panic attack
aa. Renal impairment includes Acute kidney injury, Blood creatinine increased, Renal failure
bb. Cough includes Cough, Productive cough, Upper-airway cough syndrome
cc. Dyspnea includes Dyspnoea, Dyspnoea exertional
dd. Hypoxia includes Hypoxia, Oxygen saturation decreased
ee. Nasal inflammation includes Rhinitis allergic, Rhinorrhoea
ff. Respiratory failure includes Respiratory failure, Acute respiratory failure
gg. Rash includes Rash, Dermatitis bullous, Erythema, Pruritus, Rash erythematous, Rash macular, Rash maculo-papular, Rash pustular, Stevens-Johnson syndrome, Urticaria
hh. Hypotension includes Hypotension, Capillary leak syndrome, Diastolic hypotension, Hypoperfusion, Orthostatic hypotension
ii. Thrombosis includes Thrombosis, Deep vein thrombosis, Device occlusion, Embolism, Jugular vein thrombosis, Peripheral embolism, Peripheral ischaemia, Pulmonary embolism, Splenic vein thrombosis, Subclavian vein thrombosis, Thrombosis in device, Vascular occlusion

Description of selected adverse reactions from ZUMA-1 and ZUMA-5

Cytokine release syndrome
CRS occurred in 93% of patients in ZUMA-1 and 77% of patients in ZUMA-5. Eleven percent (11%) of patients in ZUMA-1 and 6% of patients in ZUMA-5 experienced Grade 3 or higher (severe, life-threatening, and fatal) CRS. The median time to onset was 2 days (range: 1 to 12 days) for patients in ZUMA-1 and 4 days (range: 1 to 11 days) for patients in ZUMA-5, and the median duration was 7.5 days (range: 2 to 29 days, with the exception of one outlying observation of 58 days) for patients in ZUMA-1 and 6 days (range: 1 to 27 days) for patients in ZUMA-5. Ninety-eight percent (98%) of patients in ZUMA-1 and 99% of patients in ZUMA-5 recovered from CRS.

The most common signs or symptoms associated with CRS included pyrexia (90%), hypotension (42%), hypoxia (23%), chills (23%), tachycardia (17%) and sinus tachycardia (17%). Serious adverse reactions that may be associated with CRS included pyrexia (5%), hypoxia (3%), hypotension (1%), acute kidney injury (1%), atrial fibrillation (1%), atrial flutter (1%) and ejection fraction decrease (1%). See section 4.4 for monitoring and management guidance.

Neurologic adverse reactions
Neurologic adverse reactions occurred in 66% of patients in ZUMA-1 and 57% of patients in ZUMA-5. Thirty-one percent (31%) of patients in ZUMA-1 and 16% of patients in ZUMA-5 experienced Grade 3 or higher (severe or life-threatening) adverse reactions. Neurologic toxicities occurred within the first 7 days of infusion for 93% of patients in ZUMA-1 and 65% of patients in ZUMA-5. The median time to onset was 5 days (range: 1 to 17 days) for patients in ZUMA-1 and 7 days (range: 1 to 177 days) for patients in ZUMA-5. The median duration was 13 days in ZUMA-1 and 14 days in ZUMA-5, with resolution occurring within 3 weeks for 61% and 60% of patients respectively, following infusion.

The most common signs or symptoms associated with neurologic adverse reactions included tremors (30%), encephalopathy (28%), confusional state (25%), aphasia (15%), and somnolence (12%). Serious neurologic adverse reactions reported in patients who were administered Yescarta included encephalopathy (12%), confusional state (5%), aphasia (3%), agitation (2%), somnolence (2%) and delirium (1%).

Other neurologic adverse reactions have been reported less frequently in clinical trials and included dysphagia (5%), myelitis (0.2%), and quadriplegia (0.2%).

Adverse reactions reported in the post-marketing setting include status epilepticus (0.4%), spinal cord oedema and ICANS which were reported in the context of neurologic toxicity.

See section 4.4 for monitoring and management guidance.

Febrile neutropenia and infections
Febrile neutropenia was observed in 16% of patients after Yescarta infusion. Infections occurred in 50% of patients. Grade 3 or higher (severe, life-threatening, or fatal) infections occurred in 22% of patients. Grade 3 or higher unspecified pathogen, bacterial, and viral infections occurred in 15%, 7%, and 5% of patients respectively. The most common site of infection was in the respiratory tract. See section 4.4 for monitoring and management guidance.

Prolonged cytopenias
Grade 3 or higher neutropenia , anaemia, and thrombocytopenia occurred in 60%, 32%, and 29% of patients, respectively. Prolonged (still present at Day 30 or with an onset at Day 30 or beyond) Grade 3 or higher neutropenia, thrombocytopenia, and anaemia occurred in 26%, 16%, and 8% of patients, respectively. In ZUMA-1, Grade 3 or higher neutropenia, thrombocytopenia, and anaemia present after Day 93 occurred in 11%, 7%, and 3% of patients, respectively. See section 4.4 for management guidance.

Hypogammaglobulinaemia
Hypogammaglobulinaemia was reported in 16% of patients treated with Yescarta. Cumulatively, 36 (33%) of 108 subjects in ZUMA-1 received intravenous immunoglobulin therapy at the time of the 54-month analysis, and 32 (27%) of 119 subjects in ZUMA-5 received intravenous immunoglobulin therapy at the time of the 24-month follow-up analysis. See section 4.4 for management guidance.

Immunogenicity

The immunogenicity of Yescarta has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. Three out of 106 patients in ZUMA-1 preliminary tested positive via an ELISA screen for anti-FMC63 antibodies prior to being treated with Yescarta. In ZUMA-5, 13 out of 116 patients preliminary tested positive for antibodies in the ELISA screen prior to being treated with Yescarta, and 2 subjects who had negative results prior to treatment had positive test results after treatment. Results of a confirmatory cell-based assay demonstrated that all patients treated with Yescarta and had an ELISA positive result were antibody negative by the confirmatory assay, before, during and after treatment. An impact of these antibodies on efficacy or safety was not discernible.

Special population

There is limited experience with Yescarta in patients ≥ 75 years of age. Generally, safety and efficacy were similar between patients ≥ 65 years and patients < 65 years of age treated with Yescarta. Outcomes were consistent between patients with Eastern Cooperative Oncology Group (ECOG) of 0 and 1 and by sex.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There are no data regarding the signs of overdose with Yescarta.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XX70

Mechanism of action

Yescarta, an engineered autologous T-cell immunotherapy product, binds to CD19 expressing cancer cells and normal B-cells. Following anti-CD19 CAR T-cell engagement with CD19 expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signalling cascades that lead to T-cell activation, proliferation, acquisition of effector functions, and secretion of inflammatory cytokines and chemokines. This sequence of events leads to apoptosis and necrosis of CD19-expressing target cells.

Pharmacodynamic effects

In phase 2 of ZUMA-1 and ZUMA-5, after Yescarta infusion, pharmacodynamic responses were evaluated over a 4-week interval by measuring transient elevation of cytokines, chemokines, and other molecules in blood. Levels of cytokines and chemokines such as IL-6, IL-8, IL-10, IL-15, TNF-α, IFN-γ, and IL2Rα were analyzed. Peak elevation was observed within the first 14 days after infusion, and levels generally returned to baseline within 28 days.

Due to the on-target, off-tumour effect of Yescarta, a period of B-cell aplasia is expected following treatment. Among 73 DLBCL and PMBCL patients with evaluable samples at baseline, 40% had detectable B-cells; the B-cell aplasia observed in the majority of patients at baseline was attributed to prior therapies. Following Yescarta treatment, the proportion of patients with detectable B-cells decreased: 20% had detectable B-cells at Month 3, and 22% had detectable B-cells at Month 6. The initiation of B-cell recovery was first noted at Month 9, when 56% of patients had detectable B-cells. This trend of B-cell recovery continued over time, as 64% of patients had detectable B-cells at Month 18, and 77% of patients had detectable B-cells at Month 24. Patients were not required to be followed after they progressed; thus, the majority of patients with evaluable samples were responders. Among 113 FL patients with evaluable samples at baseline, 75% of patients had detectable B-cells. Following Yescarta treatment, the proportion of patients with detectable B-cells decreased: 40% of patients had detectable B-cells at Month 3. B-cell recovery was observed over time, with 61% of patients had detectable B-cells at Month 24.

Analyses performed to identify associations between cytokine levels and incidence of CRS or neurologic events showed that higher levels (peak and AUC at 1 month) of inflammatory serum analytes including IL-6, were correlated with Grade 3 or higher neurologic events and Grade 3 or higher CRS. Higher levels of multiple serum analytes including IL-15 were associated with Grade 3 or higher neurologic events and Grade 3 or higher CRS in ZUMA-1 and were associated with Grade 3 or higher CRS in ZUMA-5.

Clinical efficacy and safety

DLBCL, PMBCL and DLBCL arising from follicular lymphoma (ZUMA-1)
A total of 108 patients were treated with Yescarta in a phase 1/2 open-label, multicentre, single-arm study in patients with relapsed or refractory aggressive B-cell NHL. Efficacy was based on 101 patients in phase 2, including histologically confirmed DLBCL (N = 77), PMBCL (N = 8), or DLBCL arising from follicular lymphoma, (N = 16) based on the 2008 WHO-classification. DLBCL in ZUMA-1 included patients with DLBCL NOS, other DLBCL subtypes, and high-grade B-cell

lymphoma (HGBCL) based on the 2016 WHO-classification. Forty-seven patients were evaluable for MYC, BCL-2, and BCL-6 status. Thirty were found to have double expressor DLBCL (overexpression of both MYC and BCL-2 protein); 5 were found to have HGBCL with MYC, BCL-2 or BCL-6 gene rearrangement (double- and triple-hit); and 2 were found to have HGBCL not otherwise specified. Sixty-six patients were evaluable for cell-of-origin classifications (germinal center B-cell type [GCB] or activated B-cell type [ABC]). Of these, 49 patients had GCB-type and 17 patients had ABC-type.

Eligible patients were ≥ 18 years of age with refractory disease defined as progressive disease (PD) or stable disease (SD) as best response to last line of therapy, or disease progression within 12 months after autologous stem cell transplant (ASCT). Patients who were refractory to chemotherapy or who relapsed after two or more lines of systemic therapy were generally ineligible for haematopoietic stem cell transplantation. Patients must have received at least prior anti-CD20 antibody therapy and an anthracycline containing regimen. Patients with CNS lymphoma, a history of allogeneic stem cell transplantation (SCT) or prior anti-CD19 CAR or other genetically modified T-cell therapy were excluded. Patients with a history of CNS disorders (such as seizures or cerebrovascular ischemia), cardiac ejection fraction of less than 50% or room air oxygen saturation of less than 92%, or autoimmune disease requiring systemic immunosuppression were ineligible. The median duration of follow-up was 63.1 months (still ongoing). A summary of the patient demographics is provided in Table 4.

Table 4: Summary of demographics for ZUMA-1 phase 2 (12 month analysis)

Category	**All leukapheresed (ITT) Cohort 1 + 2 (N = 111)**	**All treated (mITT) Cohort 1 + 2 (N = 101)**
Age (years)		
Median (min, max)	58 (23, 76)	58 (23, 76)
≥ 65	23%	24%
Male gender	69%	67%
Race		
White	85%	86%
Asian	4%	3%
Black	4%	4%
ECOG status		
ECOG 0	41%	42%
ECOG 1	59%	58%
Median number of prior therapies (min, max)	3 (1, 10)	3 (1, 10)
Patients with refractory disease to ≥ 2 prior lines of therapy	77%	76%
Patients relapsed within 1 year of ASCT	20%	21%
Patients with International Prognostic Index 3/4	46%	46%
Patients with disease stage III/IV	85%	85%

Yescarta was administered as a single infusion at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg after lymphodepleting chemotherapy regimen of 500 mg/m^2 intravenous cyclophosphamide and 30 mg/m^2 intravenous fludarabine on the 5th, 4th, and 3rd day before Yescarta. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was not permitted. All patients were hospitalized for observation for a minimum of 7 days after Yescarta infusion.

Of 111 patients who underwent leukapheresis, 101 received Yescarta. Nine patients were not treated, primarily due to progressive disease or serious adverse events after enrolment and prior to cell delivery. One out of 111 patients did not receive the product due to manufacturing failure. The median time from leukapheresis to product delivery was 17 days (range: 14 to 51 days), and the median time from leukapheresis to infusion was 24 days (range: 16 to 73 days). The median dose was 2.0 x 10^6 anti-CD19 CAR T cells/kg. ITT was defined as all patients who underwent leukapheresis; mITT was defined as all patients who received Yescarta.

The primary endpoint was objective response rate (ORR). Secondary endpoints included duration of response (DOR), overall survival (OS), and severity of adverse events. The ORR was prespecified to be tested in the first 92 treated patients and was significantly higher than the prespecified rate of 20% ($P < 0.0001$).

In the primary analysis, based on the mITT population (minimum follow-up of 6 months) the ORR was 72% and the complete response (CR) rate was 51%, as determined by an independent review committee. In the 12 month followup analysis (Table 5), the ORR was 72% and the CR rate was 51%. The median time to response was 1.0 months (range: 0.8 to 6.3 months). The DOR was longer in patients who achieved CR, as compared to patients with a best response of partial response (PR). Of the 52 patients who achieved CR, 7 patients had SD and 9 had PR at their initial tumour assessment and converted to CR as late as 6.5 months. The ORR results within PMBCL and DLBCL arising from follicular lymphoma were both 88%. CR rates were 75% and 56%, respectively. Of the 111 patients in the ITT population, the ORR was 66% and the CR was 47%. Other outcomes were consistent with those of the mITT population.

In the 24-month follow-up analysis, based on the mITT population (results from an independent review committee), the ORR and the CR rate were 74% and 54%, respectively. The median time to response was 1.0 months (range: 0.8 to 12.2 months). The DOR was longer in patients who achieved CR compared to patients with a best response of PR (Table 5). Of the 55 patients who achieved CR, 7 patients had SD and 10 had PR at their initial tumour assessment and converted to CR as late as 12 months after Yescarta infusion. Median duration of response and median overall survival had not been reached (Table 5). In a 36-month analysis (median study follow-up of 39.1 months) the median overall survival was 25.8 months with 47 patients (47%*) still alive. In a 48-month analysis (median study follow-up of 51.1 months) the median overall survival was 25.8 months with 43 patients (44%*) still alive. In a 60-month analysis (median study follow-up of 63.1 months) the median overall survival was 25.8 months with 42 patients (43%*) still alive.
*The Kaplan-Meier estimates of the 3-year,4-year and 5-year OS rates were 47%, 44% and 43% respectively.

In the phase 1 part of ZUMA-1, 7 patients were treated. Five patients responded, including 4 CRs. At the 12-month follow-up analysis, 3 patients remained in CR 24 months after Yescarta infusion. At the 24-month follow-up analysis, these 3 patients remained in CR at 30 to 35 months after Yescarta infusion.

Table 5. Summary of efficacy results for ZUMA-1 phase 2

Category	**All leukapheresed (ITT) Cohort 1 + 2 (N = 111)**		**All treated (mITT) Cohort 1 + 2 (N = 101)**	
	12-month analysis	**24-month analysis**	**12-month analysis**	**24-month analysis**
ORR (%) [95% CI]	66 (56, 75)	68 (58, 76)	72 (62, 81)	74 (65, 82)
CR (%)	47	50	51	54
Duration of Response[a], median (range) in months	14.0 (0.0, 17.3)	NE (0.0, 29.5)	14.0 (0.0, 17.3)	NE (0.0, 29.5)
Duration of Response[a], CR, median (range) in months	NE (0.4, 17.3)	NE (0.4, 29.5)	NE (0.4, 17.3)	NE (0.4, 29.5)
Overall Survival, median (months) [95% CI]	17.4 (11.6, NE)	17.4 (11.6, NE)	NE (12.8, NE)	NE (12.8, NE)
6 month OS (%) [95% CI]	81.1 (72.5, 87.2)	81.1 (72.5, 87.2)	79.2 (69.9, 85.9)	79.2 (69.9, 85.9)
9 month OS (%) [95% CI]	69.4 (59.9, 77.0)	69.4 (59.9, 77.0)	69.3 (59.3, 77.3)	69.3 (59.3, 77.3)
12 month OS (%) [95% CI]	59.3 (49.6, 67.8)	59.5 (49.7, 67.9)	60.4 (50.2, 69.2)	60.4 (50.2, 69.2)
24 month OS (%) [95% CI]	Not applicable	47.7 (38.2, 56.7)	Not applicable	50.5 (40.4, 59.7)

NE= Not estimable (not reached)
a. Duration of response was censored at the time of SCT for subjects who received SCT while in response.
Note: The 12-month analysis had a median follow-up of 15.1 months. The 24-month analysis had a median follow-up of 27.1 months. OS relates to the time from the leukapheresis date (ITT) or Yescarta infusion (mITT) to death from any cause.

SCHOLAR-1
A retrospective, patient-level, pooled analysis of outcomes in refractory aggressive NHL (N = 636) was conducted (Crump et al., 2017) to provide confirmation of the prespecified control response rate of 20% and historical context for interpreting the ZUMA-1 results. The analysis included patients who had not responded (SD or PD) to their last line of therapy, or had relapsed within 12 months after ASCT. Response and survival after treatment with available standard-of-care therapy was evaluated. The ORR was 26% [95% CI (21, 31)] and the CR rate was 7% [95% CI (3, 15)], with a median OS of 6.3 months.

Relapsed or refractory FL (ZUMA-5)
The efficacy and safety of Yescarta in adult patients with FL, who were treated with Yescarta, were evaluated in a phase 2 single-arm, open-label, multicentre study in patients with relapsed or refractory FL based on 2016 WHO-classification.

Eligible patients were ≥ 18 years of age with refractory disease after 2 or more prior lines of therapy. Prior therapy must have included an anti-CD20 monoclonal antibody combined with an alkylating agent (single-agent anti-CD20 antibody did not count as line of therapy for eligibility). Patients with stable disease (SD) (without relapse) > 1 year from completion of last therapy were not considered eligible. Patients with CNS lymphoma, a history of allogeneic stem cell transplantation (SCT) or prior anti-CD19 CAR or other genetically modified T-cell therapy were excluded. Patients with a history of CNS disorders (such as seizures or cerebrovascular ischemia), left ventricular ejection fraction of less than 50% or room air oxygen saturation of less than 92%, or autoimmune disease requiring systemic immunosuppression were ineligible. The study excluded patients with active or serious infections and patients with FL Grade 3b. The actual duration of follow-up was 25.9 months (range: 0.3 to 44.3 months, still ongoing). A summary of the patient demographics is provided in Table 6.

At the time of the primary analysis, a total of 122 FL patients were enrolled (i.e. *leukapheresed*), including 75 patients who had received 3 or more lines of previous therapy. In the period between the primary analysis data cut-off date and the 24-month follow-up analysis data cut-off date, no additional subjects with FL were enrolled or treated with Yescarta.

Table 6: Summary of demographics for ZUMA-5 FL patients (24-month analysis)

Category	**All leukapheresed (N = 122)**	**All leukapheresed with ≥ 3 lines of therapy (N = 75*)**
Age (years)		
Median (min, max)	60 (34, 79)	60 (34, 79)
≥ 65	30%	31%
Male gender	60%	63%
Race		
White	93%	93%
Asian	2%	4%
Black	2%	1%
ECOG status		
0	63%	59%
1	37%	41%
High tumour bulk as defined by GELF criteria	52%	57%
Median number of prior therapies (min, max)	3 (1, 10)	4 (3, 10)
Patients with refractory disease to ≥ 2 prior lines of therapy	30%	24%
Patients with disease stage III/IV	86%	86%
Patients with prior autologous stem cell transplant	25%	29%

Category	All leukapheresed (N = 122)	All leukapheresed with ≥ 3 lines of therapy (N = 75*)
Prior PI3K inhibitor	26%	40%
Time to relapse from first anti-CD20 chemotherapy combination therapy < 24 months	54%	51%

* All subjects with locally confirmed diagnosis, including 60 subjects with centralised confirmed diagnosis. Number of leukapheresed (n=75) and treated (n=73) subjects.

Yescarta was administered as a single intravenous infusion at a target dose of 2×10^6 anti-CD19 CAR T cells/kg after lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously, both given on the 5th, 4th, and 3rd day before Yescarta. All patients were hospitalized for observation for a minimum of 7 days after Yescarta infusion. The administration and monitoring of Yescarta is consistent between ZUMA-5 and ZUMA-1.

The primary analysis was performed, when at least 80 consecutively enrolled FL patients had a minimum follow-up of 12 months from first response assessment. The primary endpoint was ORR. Secondary endpoints included CR rate, ORR and CR in subjects who received 3 or more lines of prior therapy, DOR, OS and progression free survival (PFS) and incidence of adverse events. Three out of the 122 FL patients enrolled at the time of the primary analysis were not treated, primarily due to ineligibility, experiencing CR prior or death prior to the treatment.
A 24-month follow-up analysis was performed, when at least 80 FL patients had a minimum follow-up of 24 months after infusion.

As of the 24-month follow-up analysis, no additional patients underwent leukapheresis nor were treated with Yescarta. No manufacturing failures occurred. The median time from leukapheresis to product release was 12 days (range: 10 to 37 days), leukapheresis to product delivery was 17 days (range: 13 to 72 days) and leukapheresis to Yescarta infusion was 27 days (range: 19 to 330 days). The median dose was 2.0×10^6 anti-CD19 CAR T cells/kg.
At the time of the primary analysis data cut, 122 FL patients were enrolled. Among the 75 enrolled FL patients who had 3 or more lines of prior therapy, the ORR was 91% and the CR rate was 77%.

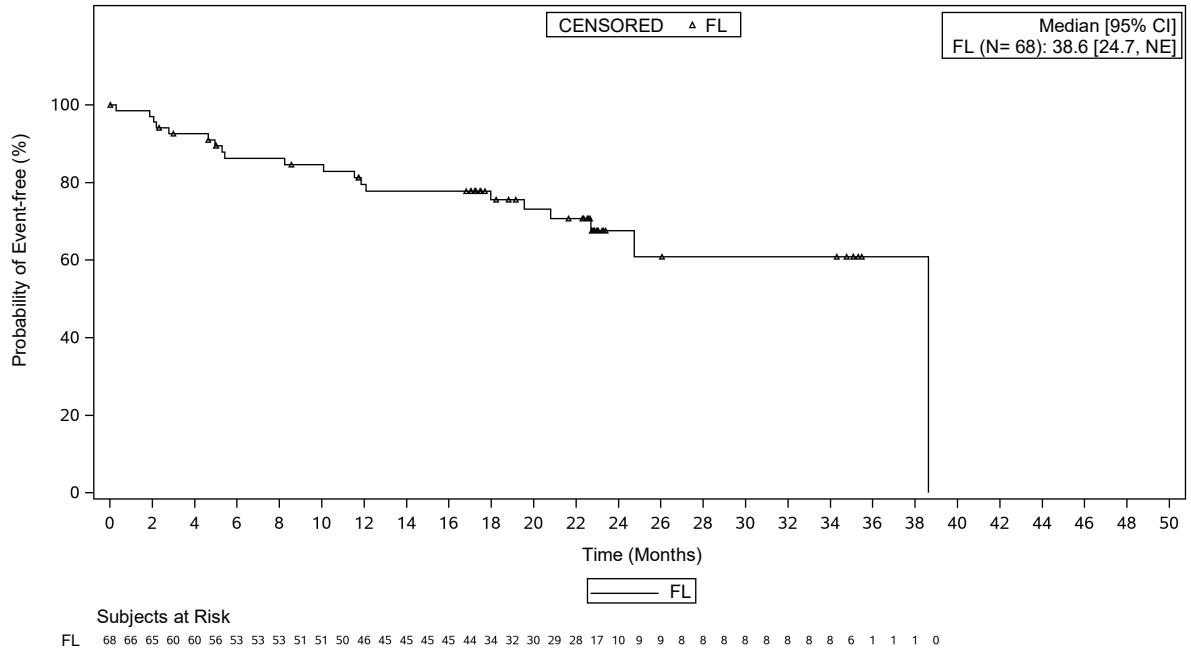
The 24-month follow-up analysis was performed on the 122 enrolled FL patients, and 119 of these patients were treated with Yescarta. Among the 122 enrolled FL patients, 75 had 3 or more lines of prior therapy, resulting in an ORR of 91% and CR rate of 77%. The median time to response was 1 month (range: 0.8 to 3.1 months), the median DOR was 38.6 months and the proportion of responders who remained in response was 56% at Month 24. Twenty nine out of 75 FL patients who had 3 or more prior lines of therapy initially achieved a PR, 19 of whom later achieved CR. Subgroup analysis included ORR in patients who were refractory (88%), FLIPI score ≥3 (94%), high tumour burden (91%), progression of disease within 24 months of first immunotherapy (89%) and prior treatment with PI3K inhibitor (90%). Key efficacy results for FL patients with 3 or more prior lines of therapy are summarized in Table 7.

Table 7. Summary of Efficacy Results for all enrolled ZUMA-5 FL patients with 3 or more prior lines of therapy (24-month analysis)

Category	All leukapheresed (ITT) N = 75*
ORR[a], (%) [95% CI]	91% (82, 96)
CR, (%)	77%
PR, (%)	13%
Duration of Response[b], median in months [95% CI] (range)	38.6 (24.7, NE) (0.0, 38.6)
Ongoing Response (n)	42
Rate of Continued Remission[b] % [95% CI] 12 Month 18 Month 24 Month	 79.5(67.2, 87.6) 75.5 (62.5, 84.6) 67.6 (52.7, 78.7)

CI, confidence interval; NE, not estimable; ORR, objective response; CR, complete response; PR, partial response.
a. Per the International Working Group Lugano Classification (Cheson 2014), as assessed by the Independent Radiology Review Committee.
b. Measured from the date of first objective response to the date of progression or death.
* All subjects with locally confirmed diagnosis, including 60 subjects with centralized confirmed diagnosis. Number of leukapheresed (n=75) and treated (n=73) subjects.

Figure 1 Kaplan Meier DOR in the all leukapheresed set, subjects with objective response (FL patients with 3 or more lines of prior therapy, 24-month analysis, independent review committee)



5.2 Pharmacokinetic properties

Peak levels of anti-CD19 CAR T cells occurred within the first 8 to 15 days after Yescarta infusion. Among patients with DLBCL, the median peak level of anti-CD19 CAR T cells in the blood (C_{max}) was 38.3 cells/µL (range: 0.8 to 1513.7 cells/µL), which decreased to a median of 2.1 cells/µL by 1 month (range: 0 to 167.4 cells/µL) and to a median of 0.4 cells/µL by 3 months (range: 0 to 28.4 cells/µL) after Yescarta infusion. Among patients with FL, the median peak level of anti-CD19 CAR T cells in the blood (C_{max}) was 37.6 cells/µL (range: 0.5 to 1415.4 cells/µL). The median time to peak of anti-CD19 CAR T cells in the blood was 8 days after infusion (range: 8 to 371 days). By 3

months, anti-CD19 CAR T cell levels decreased to near baseline levels to a median of 0.3 cells/µL (range: 0 to 15.8 cells/µL).

Age (range: 23 to 76 years) and sex had no significant impact on AUC and C_{max} of Yescarta.

Among patients with DLBCL and PMBCL,the number of anti-CD19 CAR T cells in the blood was positively associated with objective response (CR or PR). The median anti-CD19 CAR T cell C_{max} level in responders (N = 71) was 216% higher compared to the corresponding level in nonresponders (N = 25) (43.6 cells/µL *versus* 20.2 cells/µL). Median $AUC_{Day\ 0\text{-}28}$ in responding patients (N = 71) was 253% of the corresponding level in nonresponders (N = 25) (562.0 days x cells/µL *versus* 222.0 days x cells/µL).

Among patients with FL, the median peak anti-CD19 CAR T-cell levels in responders (n=112) versus nonresponders (n=5) were 38.0 cells/µL and 31.3 cells/µL, respectively. The median $AUC_{0\text{-}28}$ in responders versus nonresponders were 454.8 cells/µL•days and 247.1 cells/µL•days, respectively.

Yescarta comprises human autologous T cells. The anticipated metabolic products are typical cellular degradation products resulting from normal cellular clearance mechanisms. Thus, the infused CAR T cells are expected to be cleared over time.

Studies of Yescarta in patients with hepatic and renal impairment were not conducted.

5.3 Preclinical safety data

Yescarta comprises engineered human T cells, therefore there are no representative *in vitro* assays, *ex vivo* models, or *in vivo* models that can accurately address the toxicological characteristics of the human product. Hence, traditional toxicology studies used for drug development were not performed.

No carcinogenicity or genotoxicity studies have been conducted with Yescarta.

No studies have been conducted to evaluate the effects of Yescarta on fertility, reproduction, and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cryostor CS10
Sodium chloride
Human albumin

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Yescarta is stable for 1 year when stored frozen in the vapour phase of liquid nitrogen (≤ -150 ˚C).

The stability of Yescarta upon completion of thawing is up to 3 hours at room temperature (20 ˚C to 25 °C). However, Yescarta infusion must begin within 30 minutes of thaw completion and the total Yescarta infusion time should not exceed 30 minutes. Thawed product must not be refrozen.

6.4 Special precautions for storage

The Yescarta bag must be stored in the vapour phase of liquid nitrogen (≤ -150 ˚C) and Yescarta must remain frozen until the patient is ready for treatment to ensure viable live autologous cells are administered to the patient.

For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Ethylene-vinyl acetate cryostorage bag with sealed addition tube and two available spike ports, containing approximately 68 mL of cell dispersion.

One cryostorage bag is individually packed in a shipping cassette.

6.6 Special precautions for disposal and other handling

Irradiation could lead to inactivation of the product.

Precautions to be taken for transport and disposal of the medicinal product

Yescarta must be transported within the facility in closed, break-proof, leak-proof containers.

Yescarta contains genetically-modified human blood cells. Local guidelines on handling of waste of human-derived material mustbe followed for unused medicinal products or waste material. All material that has been in contact with Yescarta (solid and liquid waste) mustbe handled and disposed of in accordance with local guidelines on handling of waste of human-derived material.

Accidental exposure to Yescarta must be avoided. Local guidelines on handling of waste of human derived-materials mustbe followed in case of accidental exposure, which may include washing of the contaminated skin, and removal of contaminated clothes. Work surfaces and materials which have potentially been in contact with Yescarta must be decontaminated with appropriate disinfectant.

7. MARKETING AUTHORISATION HOLDER

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1299/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 August 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Kite Pharma, Inc.
2355 Utah Avenue
El Segundo
California
CA 90245
United States

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

Name and address of the manufacturer responsible for batch release

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSUR)**

The requirements for submission of PSUR for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Key elements:

Availability of tocilizumab and site qualification

The MAH will ensure that hospitals and their associated centres that dispense Yescarta are qualified in accordance with the agreed controlled distribution programme by:
- ensuring immediate, on-site access to one dose of tocilizumab per patient prior to Yescarta infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensuring that suitable alternative measures to treat CRS instead of tocilizumab are available on-site.
- ensuring healthcare professionals (HCP) involved in the treatment of a patient have completed the educational programme.

Educational program – Prior to the launch of Yescarta in each Member State the MAH must agree the content and format of the educational materials with the National Competent Authority.

HCP Educational program

The MAH shall ensure that in each Member State where Yescarta is marketed, all HCPs who are expected to prescribe, dispense, and administer Yescarta shall be provided with a guidance document to:
- facilitate identification of CRS and serious neurologic adverse reactions
- facilitate management of the CRS and serious neurologic adverse reactions
- ensure adequate monitoring of CRS and serious neurologic adverse reactions
- facilitate provision of all relevant information to patients
- ensure that adverse reactions are adequately and appropriately reported
- ensure that detailed instructions about the thawing procedure are provided
- before treating a patient, ensure that at least 1 dose of tocilizumab for each patient is available on site; in the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicine Agency shortage catalogue, ensure that suitable alternative measures to treat CRS are available on site

Patient Educational program

To inform and explain to patients
- the risks of CRS and serious neurologic adverse reactions, associated with Yescarta
- the need to report the symptoms to their treating doctor immediately
- the need to remain in the proximity of the location where Yescarta was received for at least 4 weeks following Yescarta infusion
- the need to carry the patient alert card at all times

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Non-interventional post-authorisation safety study (PASS): In order to assess the safety profile including long term safety in patients with B-lymphocyte malignancies treated with axicabtagene ciloleucel in the post marketing setting, the applicant should conduct and submit a study based on a registry.	•Update reports: Annual safety reports and 5-yearly interim reports •Final report of study results: December 2038

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CONTAINER (CASSETTE)

1. NAME OF THE MEDICINAL PRODUCT

Yescarta 0.4 – 2 x 10^8 cells dispersion for infusion
axicabtagene ciloleucel (CAR+ viable T cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor (CAR) with a target dose of 2 x 10^6 anti-CD19 CAR-positive viable T cells/kg.

3. LIST OF EXCIPIENTS

Excipients: Cryostor CS10, human albumin, sodium chloride. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
One sterile infusion bag.
Contents: approximately 68 mL of cell dispersion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Do not irradiate.
For intravenous use only.
Gently mix the contents of the bag while thawing.
Do NOT use a leukodepleting filter.
STOP confirm patient ID prior to infusion.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only.

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store frozen in vapour phase of liquid nitrogen ≤ -150˚C.
Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Contains genetically-modified human blood cells.
Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kite Pharma EU B.V.
Tufsteen 1
2132 NT Hoofddorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1299/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot:
Kite Patient ID:
Additional Patient ID:
Patient Name:
Patient DOB:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INFUSION BAG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Yescarta 0.4 – 2 x 10^8 cells dispersion for infusion
axicabtagene ciloleucel (CAR+ viable T cells)
For intravenous use only.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot:
Kite Patient ID:
Additional Patient ID:
Patient Name:
Patient DOB:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

One sterile infusion bag.
Contents: approximately 68 mL of cell dispersion.

6. OTHER

For autologous use only.
Verify patient ID.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Yescarta 0.4 – 2 x 10^8 cells dispersion for infusion
axicabtagene ciloleucel (CAR+ viable T cells)

▢ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- Your doctor will give you a Patient Alert Card. Read it carefully and follow the instructions on it.
- Always show the Patient Alert Card to the doctor or nurse when you see them or if you go to hospital.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Yescarta is and what it is used for

Yescarta is a gene therapy medicine used for treating adults with aggressive diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma (FL) affecting your lymph tissue (part of the immune system) that affects a type of white blood cell called B lymphocytes and other organs in your body. Too many of these abnormal white blood cells accumulate in your tissue and this is the cause of the symptoms you may have. It is used to treat these conditions when other available medicines have stopped working for you.

The medicine is made specially for you as a single administration of your own modified white blood cells. It is given by a drip (*infusion*) into a vein (*intravenously*).

2. What you need to know before you are given Yescarta

You must not be given Yescarta if you are allergic to any of the ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.

Warnings and precautions

Yescarta is made from your own white blood cells and must only be given to you (*autologous use*).

Before you are given Yescarta you must tell your doctor if you:

- have problems with your nervous system (such as fits, stroke, or memory loss).
- have kidney problems.
- have low blood cell levels (blood counts).

- have had a stem cell transplant in the last 4 months.
- have any lung, heart or blood pressure (low or raised) problems.
- have signs or symptoms of graft-versus-host disease. This happens when transplanted cells attack your body, causing symptoms such as rash, nausea, vomiting, diarrhoea and bloody stools.
- notice the symptoms of your cancer are getting worse. If you have lymphoma this might include fever, feeling weak, night sweats, sudden weight loss.
- have an infection. The infection will be treated before the Yescarta infusion.
- have had hepatitis B, hepatitis C or human immunodeficiency virus (HIV) infection.

If any of the above apply to you (or you are not sure), talk to your doctor before being given Yescarta.

Tests and checks

Before you are given Yescarta your doctor will:
- Check your lungs, heart and blood pressure.
- Look for signs of infection; any infection will be treated before you are given Yescarta.
- Check if your cancer is getting worse.
- Look for signs of graft-versus-host disease that can happen after a transplant.
- Check your blood for uric acid and for how many cancer cells there are in your blood. This will show if you are likely to develop a condition called tumour lysis syndrome. You may be given medicines to help prevent the condition.
- Check for hepatitis B, hepatitis C or HIV infection.
- Check if you had a vaccination in the previous 6 weeks or are planning to have one in the next few months.

After you have been given Yescarta

Tell your doctor or nurse immediately if you have any of the following:
- Chills, extreme tiredness, weakness, dizziness, headache, cough, shortness of breath, or rapid heartbeat, which may be symptoms of a condition known as cytokine release syndrome. Take your temperature twice a day for 3-4 weeks after treatment with Yescarta. If your temperature is high, see your doctor immediately.
- Fits, shaking, or difficulty speaking or slurred speech, loss of consciousness or decreased level of consciousness, confusion and disorientation, loss of balance or coordination.
- Fever, which may be a symptom of an infection.
- Extreme tiredness, weakness and shortness of breath, which may be symptoms of a lack of red blood cells.
- Bleeding or bruising more easily, which may be symptoms of low levels of cells in the blood known as platelets.

Your doctor will regularly check your blood counts as the number of blood cells and other blood components may decrease.

Do not donate blood, organs, tissues or cells for transplants.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before you are given Yescarta. Your doctor may need to take special care of you during your treatment with Yescarta.

In some cases, it might not be possible to go ahead with the planned treatment with Yescarta. For example:

- If Yescarta infusion is delayed for more than 2 weeks after you have received preparatory chemotherapy you may have to receive more preparative chemotherapy.

Children and adolescents

Yescarta must not be used in children and adolescents below 18 years of age.

Other medicines and Yescarta

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

Before you are given Yescarta tell your doctor or nurse if you are taking any medicines that weaken your immune system such as corticosteroids, since these medicines may interfere with the effect of Yescarta.

In particular, you must not be given certain vaccines called live vaccines:
- In the 6 weeks before you are given the short course of chemotherapy (called lymphodepleting chemotherapy) to prepare your body for the Yescarta cells.
- During Yescarta treatment.
- After treatment while the immune system is recovering.

Talk to your doctor if you need to have any vaccinations.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine. This is because the effects of Yescarta in pregnant or breast-feeding women are not known, and it may harm your unborn baby or your breast-fed child.
- If you are pregnant or think you may be pregnant after treatment with Yescarta, talk to your doctor immediately.
- You will be given a pregnancy test before treatment starts. Yescarta can only be given if the results show you are not pregnant.

Discuss pregnancy with your doctor if you have received Yescarta.

Driving and using machines

Some people may feel tired, dizzy or have some shaking after being given Yescarta. If this happens to you, do not drive or use heavy machines until at least 8 weeks after infusion or until your doctor tells you that you have completely recovered.

Yescarta contains sodium

This medicine contains 300 mg sodium (main component of cooking/table salt) in each infusion bag. This is the equivalent to 15% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Yescarta is given

Yescarta will always be given to you by a healthcare professional.

- Since Yescarta is made from your own white blood cells, your cells will be collected from you to prepare your medicine. Your doctor will take some of your blood using a catheter placed in your vein (a procedure call leukapheresis). Some of your white blood cells are separated from your blood and the rest of your blood is returned to your vein. This can take 3 to 6 hours and may need to be repeated.
- Your white blood cells are sent away to make Yescarta. It usually takes about 3 to 4 weeks to receive your Yescarta therapy but the time may vary.

Medicines given before Yescarta treatment

During the 30 to 60 minutes before you are given Yescarta you may be given other medicines. This is to help prevent infusion reactions and fever. These other medicines may include:
- Paracetamol.
- An antihistamine such as diphenhydramine.

Prior to receiving Yescarta, you will be given other medicines such as preparative chemotherapy, which will allow your modified white blood cells in Yescarta to multiply in your body when the medicine is given to you.

Your doctor or nurse will check carefully that this medicine is yours.

How you are given Yescarta

Yescarta will always be given to you by a doctor in a qualified treatment centre.

- Yescarta is given in a single dose.
- Your doctor or nurse will give you a single infusion of Yescarta through a catheter placed into your vein (*intravenous* infusion) over about 30 minutes.
- Yescarta is the genetically modified version of your white blood cells. Your healthcare professional handling the treatment will therefore take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases and will follow local guidelines on handling of waste of human-derived material to clean up or dispose of any material that has been in contact with it.

You must receive Yescarta infusion in a qualified clinical facility and be discharged only when your doctor thinks it is safe for you to go home.
Your doctor may do blood tests to check for side effects.

After you are given Yescarta

- Plan to stay within proximity from the hospital where you were treated for at least 4 weeks after you have been given Yescarta. Your doctor will recommend that you return to the hospital daily for at least 10 days and will consider whether you need to stay at the hospital as an in-patient for the first 10 days after infusion. This is so your doctor can check if your treatment is working and help you if you have any side effects.

If you miss any appointments, call your doctor or the qualified clinical facility as soon as possible to reschedule your appointment.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Yescarta can cause side effects to your immune system that may be serious or life-threatening, and can lead to death.

The following side effects have been reported with Yescarta.

Very common (may affect more than 1 in 10 people)
- Fever, chills, reduced blood pressure which may cause symptoms such as dizziness, lightheadedness, fluid in the lungs, which may be severe and can be fatal (all symptoms of a condition called *cytokine release syndrome*).
- Abnormally low number of white blood cells, which may increase your risk of infection.

- Loss of consciousness or decreased level of consciousness, confusion or memory loss due to disturbances of brain function, involuntary shaking (*tremor*), sudden confusion with agitation, disorientation, hallucination or irritability (*delirium*).
- Decrease in the number of red blood cells (*cells that carry oxygen*): symptoms can include extreme tiredness with a loss of energy.
- Extreme tiredness.
- Low number of cells that help clot the blood (*thrombocytopenia*): symptoms can include excessive or prolonged bleeding or bruising.
- Muscle and joint pain, back pain.
- Fever or chills, which may be signs of an infection.
- Headache.
- High levels of uric acid, or magnesium seen in blood tests. Low levels of sodium or phosphate, seen in blood tests.
- Nausea, constipation, diarrhoea, abdominal pain, vomiting.
- Decreased appetite, weight loss.
- Low blood pressure, dizziness.
- Shortness of breath, cough.
- Fast or slow heartbeat.
- Irregular heartbeat (*arrhythmia*).
- Low levels of immunoglobulins seen in blood test, which may lead to infections.
- Kidney problems causing your body to hold onto fluid, build-up of fluids in tissue (*oedema*) which can lead to weight gain and difficulty in breathing, decreased output of urine.
- Lack of energy or strength, muscular weakness, difficulty moving, muscle spasm.
- Skin rash or skin problems.
- Difficulty sleeping
- High blood pressure.
- Blood clots: symptoms can include pain in the chest or upper back, difficulty breathing, coughing up blood or cramping pain, swelling in a single leg, warm and darkened skin around the painful area.
- Increase in liver enzymes seen in blood tests.

Common (may affect up to 1 in 10 people)
- Dry mouth, dehydration, difficulty swallowing.
- Pain in the hands or feet.
- High levels of bilirubin seen in blood tests. Low levels of albumin, potassium or calcium seen in blood tests.
- Low oxygen level in blood.
- Failure of the kidneys causing your body to hold onto fluid which can be serious or life threatening.
- Swelling in the limbs, fluid around the lungs (*pleural effusion*).
- Lung infection.
- Alteration of the blood ability to form clots (*coagulopathy*): symptoms can include excessive or prolonged bleeding or bruising.
- Changes in vision which makes it difficult to see things (*visual impairment*).
- Pain.
- Sudden, unexpected stopping of the heart (cardiac arrest); this is serious and life-threatening.
- Heart failure.
- Fits (*seizures, including seizures that may be prolonged and life-threatening*),
- Inability to move one side of the body
- Hypersensitivity: symptoms such as rash, hives, itching, swelling and anaphylaxis.
- Mood disorders.
- Nasal inflammation.
- Weakness or inability to move on one side of the body, making it hard to perform everyday activities like eating or dressing.
- Loss of control of body movements.

Uncommon (may affect up to 1 in 100 people)
- Difficulty understanding numbers, memory loss, fits.
- Breakdown of muscle tissue that leads to the release of muscle fibre into the blood.
- Improper functioning of at least 2 organs (eg, liver, lungs and kidneys) that requires medical treatment and/or procedures to restore normal organ function.
- Inflammation and swelling of spinal cord which may cause partial or total paralysis of limbs and torso.
- Paralysis of all four limbs.
- Condition of severe systemic inflammation.
- Inability to breathe on one's own.

Tell your doctor immediately if you get any of the side effects listed above. Do not try to treat your symptoms with other medicines on your own.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Yescarta

The following information is intented for doctors only.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the container label and infusion bag.

Store frozen in vapour phase of liquid nitrogen ≤ -150 °C until thawed for use.
Do not refreeze.

This medicine contains genetically modified human blood cells. Local guidelines on handling of waste of human-derived material must be followed for unused medicinal product or waste material.
As this medicine will be given by qualified healthcare professionals, they are responsible for the correct disposal of the product. These measures will help protect the environment.

6. Contents of the pack and other information

What Yescarta contains

The active substance is axicabtagene ciloleucel. Each patient-specific single infusion bag contains a dispersion of anti-CD19 CAR T cells in approximately 68 mL for a target dose of 2 x 10^6 anti-CD19 CAR-positive viable T cells/kg.
The other ingredients (excipients) are: Cryostor CS10, sodium chloride, human albumin. See section 2 "Yescarta contains sodium".

What Yescarta looks like and contents of the pack

Yescarta is a clear to opaque, white to red dispersion for infusion, supplied in an infusion bag individually packed in a metal cassette. A single infusion bag contains approximately 68 mL of cell dispersion.

Marketing Authorisation Holder and Manufacturer
Kite Pharma EU B.V.

Tufsteen 1
2132 NT Hoofddorp
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

It is important that you read the entire content of this procedure prior to administering Yescarta.

Precautions to be taken before handling or administering the medicinal product

- Yescarta contains genetically-modified human blood cells. Local guidelines on handling of waste of human-derived material applicable for such products must be followed.
- Yescarta must be transported within the facility in closed, break-proof, leak-proof containers.
- Yescarta is prepared from autologous blood of the patient collected by leukapheresis. Patient leukapheresis material and Yescarta may carry a risk of transmitting infectious viruses to healthcare professionals (HCP) handling the product. Accordingly, HCP must employ appropriate precautions (wearing gloves and glasses) when handling leukapheresis material or Yescarta to avoid potential transmission of infectious diseases.
- Work surfaces and materials that have potentially been in contact with Yescarta must be decontaminated according to local guidelines on the handling of waste of human-derived materials.

Preparation for infusion

- Verify that the patient's identity (ID) matches the patient identifiers on the Yescarta cassette.
- The Yescarta product bag must not be removed from the metal cassette if the information on the patient-specific label does not match the intended patient.
- Once the patient's ID is confirmed, remove the Yescarta product bag from the metal cassette.
- Check that the patient information on the metal cassette label matches that on the bag label. Inspect the product bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines for handling of waste of human-derived material (or immediately contact Kite).
- Place the infusion bag inside a second bag.
- Thaw Yescarta at approximately 37 °C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Yescarta must not be washed, spun down, and/or re-suspended in new medium prior to infusion. Thawing takes approximately 3 to 5 minutes.
- Once thawed, Yescarta is stable at room temperature (20˚C - 25˚C) for up to 3 hours.
- However, Yescarta infusion must begin within 30 minutes of thaw completion.

Do NOT use a leukodepleting filter.

Administration

- The medicine must be administered in a qualified treatment centre by a physician(s) with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with Yescarta.
- Ensure that at least 1 dose of tocilizumab per patient and emergency equipment are available prior to infusion and during the recovery period. Hospitals should have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensure that suitable alternative measures to treat CRS instead of tocilizumab are available on-site.
- The patient's identity must be matched with the patient identifiers on the infusion bag.
- Yescarta is for autologous use only.
- Yescarta must be administered as an intravenous infusion using latex-free intravenous tubing without a leukocyte depleting filter within 30 minutes by either gravity or a peristaltic pump.
- Gently agitate the bag during Yescarta infusion to prevent cell clumping. All contents of the infusion bag must be infused.
- Sterile sodium chloride 9 mg/mL (0.9%) (0.154 mmol sodium per mL) solution for injection must be used to prime the tubing prior to infusion as well as rinse it afterwards. When the full

volume of Yescarta has been infused, the infusion bag must be rinsed with 10 to 30 mL sodium chloride 9 mg/mL (0.9%) solution for injection by back priming to ensure as many cells as possible are infused into the patient.

Disposal of Yescarta

- Any unused medicinal product or waste material that has been in contact with Yescarta (solid and liquid waste) must be handled and disposed in accordance with local guidelines on the handling of waste of human-derived material. Work surfaces and material which have potentially been in contact with Yescarta must be decontaminated with appropriate disinfectant.

Accidental exposure

- Accidental exposure to Yescarta must be avoided. Local guidelines on handling of waste of human-derived material must be followed in case of accidental exposure, which may include washing of the contaminated skin, and removal of contaminated clothes.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for axicabtagene ciloleucel, the scientific conclusions of CHMP are as follows:

In view of available data on status epilepticus from ongoing clinical trials, the literature, spontaneous reports including in some cases a close temporal relationship and in view of a plausible mechanism of action, the PRAC considers a causal relationship between axicabtagene ciloleucel and status epilepticus is at least a reasonable possibility. The PRAC concluded that the product information of products containing axicabtagene ciloleucel should be amended accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for axicabtagene ciloleucel the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing axicabtagene ciloleucel is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.